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10/689,122	10/20/2003	Tabassum Naqvi	3817.14-1	4234

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EXAMINER	
HAQ, SHAFIQUL	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/689,122	NAQVI ET AL.	
	Examiner	Art Unit	
	Shafiqul Haq	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,20 and 21* is/are pending in the application.

4a) Of the above claim(s) *9-17,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' amendments and arguments filed 3/19/07 is acknowledged and entered.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-3 and 5-8 are again rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for truncated extracellular portion of mouse Type1 IP_3R comprising at least amino acids sequence of 226-578, do not reasonably provide enablement for all any truncated portion (sequence) of IP_3R as binding protein which would have an affinity of at least about 200 times the affinity for IP_3 than that of intact IP_3R for IP_3.

The specification provides guidance and working examples for use of core protein or "sponge" derived from amino acid sequence 226-578 of type 1 mouse IP_3R1. But there is no enablement in the specification for use of <u>any</u> truncated portion (sequence) of IP_3R not containing the core sequence that provide high binding (200 times that that of intact IP_3R) as required by claim 1. For IP_3 binding, conserved lysine and arginine residues in N-terminal 226-576 are important (Riley et al. Journal of Biological Chemistry 2002) and first N terminal 225 residues may in fact inhibit IP3 binding (Morris et al. Biochem J. 2002). Therefore, an artisan in the art would not be able to practice the invention because an undue experimentation will be required to judge suitability of any trancated extracellular portion of IP_3R as

binding protein having binding affinity as described above. Undue experimentation would be required to practice the invention as claimed due to the quantity of experimentation necessary; limited amount of guidance and limited number of working examples in the specification; nature of the invention; state of the prior art; relative skill level of those in the art; predictability or unpredictability in the art; and breadth of the claims. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-4, 6-8 and 18-19 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Sportsman et al. (US 6,806,053 B1) in view of Iwasaki et al. (J. Biol. Chem. 2002) and Hirata et al. (J. Biol. Chem. 1990).

Sportsman et al. in a cell-signaling assay of inositos-phospholipid signaling pathway, disclose detection of intermediate 1,4, 5 IP_3 of the singnaling pathway. The assay include a tracer from the intermediate (i.e. tracer of 1,4, 5 IP_3) and a specific binding partner for 1,4,5 IP_3 (intermediate) and the tracer (e.g. labeled 1,4, 5 IP_3). Sportsman et al. also disclose that the tracer may include a luminophore attached by

a suitable chemistry to the intermediate (e.g. a fluorescein succinyl-labeled IP_3)(column 20, example 14 and figs. 5 & 6).

Sportsman et al. disclose that specific binding partner generally comprises any compound capable of specifically and competitively binding an analyte and an associated tracer and also disclose that fragments, derivatives or analogs of a preferred specific binding partner may be used (column 11, lines 22-35). Sportsman et al., however, do not disclose IP_3R receptor or fragments thereof as specific binding partner in this assay.

Iwasaki et al. disclose IP_3R antagonists that strongly and specifically bind to IP_3 (analyte). Iwasake et al. also disclose N-terminal ligand binding domain of mIP_3R1 comprising amino acid sequence 226-578 as the core region for high affinity binding to IP_3 (see page 2764, left column, lines 6-18).

Since specific binding partner for IP_3 in common and known in the art (Iwasaki et al.), it would have been obvious at the time of the invention to a person of ordinary skill in the art to include IP_3R receptor or truncated portion of the IP_3R as taught by Iwasaki et al in the assay method of Sportsman to effectively measure IP_3 in a sample with a reasonable expectation of success because specific binding partner for IP3 is envisaged in the method of Sportsman et al.

As for conjugate of IP_3 with a detectable label, Sportsman et al. disclose that the tracer may include a luminophore attached by a suitable chemistry to the intermediate (e.g. a fluorescein succinyl-labeled IP_3)(column 20, example 14) but, however, fail to disclose detectable label at the 2-hydroxy position of IP_3.

Hirata et al. disclose a series of 1,4,5-triphosphate (IP_3) analogs with substituents at 2 hydroxy position and disclose that such modification (substitution at 2-hydroxy position) do not substantially interfere with the affinity of IP_3 for IP_3 receptor (see abstrace and page 8404, right column, lines 6-13).

Therefore, given the above fact that substitution at the 2-hydoxyl position with bulky groups do not significantly alter binding affinity of IP_3 for its binding partner (Hirata et al.), it would have been obvious at the time of the invention to a person of ordinary skill in the art to attach luminophore at the 2-hydroxy position of IP_3 in the IP_3-luminophore conjugate of Sportsman et al with a reasonable expectation of success because attachment by a suitable chemistry is disclosed by Sportsman et al. and substitution at the position is preferable for not effecting IP3 binding affinity.

As for dependent claim 2, Sportsman et al. disclose that the assay may be homogeneous (column 9, lines 49-52). As for claims 4 and 6 Iwasaki disclose amino acid sequence 226-578 as the core region for high affinity binding to IP_3 and disclose a fusion protein (IP3 sponge) (page 2764, left column, lines 6-18) and as for claims 18-19, Sportsman et al. disclose component in a kit format (column 13, lines 34-35) and the packaging of components in kit form is a well-known obvious expedient for ease and convenience in assay performance and once a method has been established, one skilled in the art would clearly consider compiling in a kit format and change/modify different components of the kit to best suit the assay.

6. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sportsman et al. (US 6,806,053 B1), Iwasaki et al. (J. Biol. Chem. 2002) and Hirata et al. (J. Biol.

Chem. 1990) as applied to claims 1-4, 6-8 and 18-19 above and further in view of Henderson et al. (US 4708,929).

See above teaching for Sportsman et al., Iwasaki et al and Hirata et al in paragraph 17.

Sportsman et al. disclose IP3 conjugated with a label (e.g. luminophore) but remain silent about other label (e.g. enzyme label).

Henderson et al. in a competitive assay for protein binding disclose labeling analyte with enzyme fragment (donor enzyme fragment e.g. enzyme donor of b-galactosidase) for detection by complementation with an enzyme acceptor that results in measurable enzyme activity (abstract and column 10, line 57 through column 11, line 32). Henderson et al. also disclose that enzyme complementation is advantageous over other immunoassays employing fluorescent label as fluorescent label analyte require separation steps and are limited to small molecular weight analytes .

Since labeling analytes with enzyme fragment (enzyme donor conjugate i.e. tracer) is common and know for its sensitive detection and are not limited to small molecular analytes (Henderson et al.), it would have been obvious to one of ordinary skill in the art at the time the invention was made to use enzyme fragment (e.g. donor fragment of beta-galactosidase) to label IP_3 in the method of Sportsman et al. for detection of analytes with a reasonable expectation of success because production of enzyme fragment label conjugate and complementation assays are taught in the method of Henderson et al.

Response to Argument

7. Applicant's arguments filed 3/19/07 have fully been considered, and are persuasive to overcome the rejection under 35 USC 112, second paragraph but they are not persuasive to overcome the rejection under 35 USC 112, first paragraph and the rejections under 35 USC 103 as set forth in office action of 1/24/07.

In response to rejection under 35 USC first paragraph, Applicants instead of specifically arguing as to why applicants believe that any truncated extracellular portion of IP3R are enabled as binding protein by having at least 200 times the affinity of IP3 than that of intact IP3R for IP3, Applicants' argued that Applicants are not required to provide alternative compositions for performing their method. Applicants also argued that the invention is the method of determining 1,4,5-triphosphate inositol, not the reagent *per se*. Applicants further argued that it is not up to applicants to have to provide alternative reagents, when the reagent that is provided is adequate for the purpose of their invention. These arguments have not been found persuasive. The Examiner agree that the invention is the method of determining IP3, but Applicants must also realize that the reagent (i.e. binding protein) is a critical component in the method of detection and Applicants have not provided clear explanation with support in the specification for enablement of any truncated extracellular portion of mouse IP3R having the characteristics to be a binding protein for the assay method. Specification discloses use of core protein or "sponge" derived from amino acid sequence 226-578 of type 1 mouse IP3R as binding protein (paragraph [00041]) but specification does not disclose or give any

guidance as to what portion of IP3R receptor is considered as extracellular portion that would have the property of 200 times binding affinity for IP3 than that of intact IP3R for IP3. Except for the core amino acid sequence of 226-578 of type 1 mouse, the specification does not disclose or give any guidance for any other extracellular portion of IP3R that can be used as binding protein in the assay for measuring IP3. Furthermore, there is no disclosure or working example in the specification, even for the core amino acid sequence of 226-578 of type 1 mouse IP3R, that support **200 times** binding affinity than that of intact IP3R. Therefore, the specification does not allow anyone to practice the claimed invention without undue experimentation and thus the 35 USC 112 rejection is deemed to be appropriate.

With regard to 35 USC 103 rejections over sportsman et al., Applicants argued that Sportsman et al. do not disclose any binding protein except for allusion to an antibody. Applicants also argued that one could not have predicted that the "sponge" receptor would accept any changes in the IP3 (i.e. IP3 labeled at 2 hydoxyl position). These arguments are not found convincing.

One cannot show nonobviousness by attacking references individually wherein the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merk* & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

See *In re Fines*, 837 F.2d 1071, 5USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.1992). In this case Sportsman et al. disclose an assay for detection of IP_3 which includes a tracer (tracer i.e. a labeled IP_3) and a specific binding partner for IP_3 and the tracer. Sportsman et al. also disclose that the tracer may include a luminophore attached IP3 (e.g. a fluorescein succinyl-labeled IP_3). Sportsman et al. disclose that specific binding partner generally comprises any compound capable of specifically and competitively binding an analyte and an associated tracer and also disclose that **fragments, derivatives or analogs of a preferred specific binding partner may be used** (column 11, lines 22-35). Therefore, Sportsman et al. discloses strong motivation to involve other binding partners or fragments thereof in the assay methods. Iwasaki et al. and Hirata et al. are combined with Sportsman et al. because Iwasaki et al. disclose N-terminal 226-578 amino acid sequence of mIP3R1 binds to IP3 with high affinity and thus would be obvious to try as a binding partner as taught by Sportsman et al. and IP3 tracer having label attached to 2 hydroxy position of IP3 as taught by Hirata et al. would be obvious in the assay method of sportsman et al. because Hirata et al. disclose labels attached to 2 hydroxyl position do not substantially interfere with the affinity of IP3 for IP3 receptor. Therefore, motivation is there to combine the references.

Conclusion

8. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. The prior art made of record and not relied upon is considered pertiinent to applicant's disclosure.

Yoshikawa et al. (Biochem. Biophy. Res. Comm. 1999) disclose important region of binding domain of IP3 receptor for binding to IP3.

Riley et al. (J. Biol. Chem. 2002) disclose PEG linker at 2-hydroxyl position of IP3 more potent than IP3.

Morris et al. (Biochem. J. 2002) disclose that IP3 binding site lies within the N-terminal between residues 226 and 576 and the first 225 residues may inhibit IP3 binding.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shafiqul Haq whose telephone number is 571-272-6103. The examiner can normally be reached on 7:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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